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COMPLETE SPECIFICATION

Manufacture of Saccharide Derivatives

We, SOCIETY OF CHEMICAL INDUSTRY IN BASLE (also known as Gesellschaft für Chemische Industrie in Basle) a body corporate organised according to the Laws of Switzerland, of Basle, Switzerland, do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

Several processes for the manufacture of saccharide derivatives are known. One of the best processes is that described for the first time by W. Königs and F. Knorr (Chemische Zentralblatt, 1900, Vol. II, page 179), which consists in agitating acylhalogenoses with alcohols in the presence of agents which bind hydrogen halide, for example, silver carbonate or silver oxide. Even this process, however, leads to unsatisfactory yields, as apparently the water formed during the reaction itself reacts with the acylhalogenose. In order to prevent these secondary reactions, it has been proposed to work in the presence of agents which bind water, for example calcium chloride, calcium sulphate or calcium hydride. Nevertheless, it is only in isolated cases that any improvement in yield has been obtained in this manner.

According to the present invention, improved yields of saccharide derivatives of alicyclic and aliphatic alcohols are surprisingly obtained, even in the known process of reacting such an alcohol with an acylhalogenose in the presence of an agent capable of binding hydrogen halides and of a solvent, by continuously removing by azeotropic distillation the volatile products split off during the reaction.

As alicyclic alcohols there may be used especially alcohols of the steroid series, for example, testosterone, androsterone, corticosterone, dehydrocorticosterone, desoxycorticosterone, oestradiol or its mono-derivatives, and genins of synthetic or natural cardio-active substances. As aliphatic or other alicyclic alcohols, there may be mentioned, for example

batyl alcohol, menthol and borneol. Any acylhalogenose may be used for the manufacture of the saccharide derivatives. As agents capable of binding hydrogen halides there may be used in the usual manner, for example, silver oxide or silver carbonate.

The process is conducted in the presence of inert solvents which form azeotropic mixtures with the volatile products, for example water, which are split off during the reaction. Especially suitable solvents are, for example, methylene chloride, tetrachlorethylene, chloroform, benzene, toluene, ethyl acetate and isopropyl ether. It is of advantage to add one or both of the reaction components to the mixture containing the condensing agent at a rate corresponding with the progress of the reaction. In accordance with the invention the solvent is continuously removed by distillation at atmospheric pressure or under reduced or raised pressure, whereby the water or other volatile products split off during the reaction are continuously removed azeotropically. In this manner the secondary reactions hitherto observed are to a very great extent avoided.

The following Examples illustrate the invention, the parts being by weight:—

EXAMPLE 1.

5 parts of trans-androsterone are dissolved in 200 parts of dry benzene, then mixed with 8 parts of silver carbonate, and the whole is heated to boiling. While the benzene distils a solution of 18 parts of acetobromo-d-glucose in benzene is slowly introduced drop by drop, while stirring. When the reaction is complete, the whole is filtered with suction, the silver salts are thoroughly washed with benzene, and the clear pale yellow filtrate is evaporated under reduced pressure. The oily viscous residue is dissolved in ether, and after standing for a short time the β -d-glucoside tetracetate of trans-androsterone crystallises in the form of needles. After 24 hours, the whole is filtered with suction, and the

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page 212 (1936)] the yield of the purified tetracetyl-glucoside amounts to 25.4 per cent.

By working under reduced pressure with xylene as solvent, and heating on the boiling water bath, the yield of the purified product amounts to 3.28 parts or 46.2 per cent. of the theoretical yield. In this method of operation it is advantageous, after a little acetobromo-glucose has been introduced dropwise, to heat the whole for a short time without the application of reduced pressure, until the liberation of carbon dioxide begins. It is also advantageous to heat the whole at the close of the reaction for a further $\frac{1}{2}$ hour, without the application of reduced pressure in order to cause the last traces of acetobromo-glucose to react.

20. **EXAMPLE 4.**
10 parts of desoxycorticosterone and 13 parts of silver carbonate are mixed with 400 parts of absolute chloroform in a three-necked flask fitted with a stirrer, dropping funnel and a reflux condenser, and the solution is heated to boiling. While the chloroform distils, a solution of 25 parts of acetobromo-*d*-glucose in 500 parts of chloroform is slowly added drop by drop while stirring. The whole is then heated for a further $\frac{1}{2}$ hour, the silver salts are separated by filtration, and washed with chloroform, and the filtrate is evaporated under reduced pressure. The viscous residue is dissolved in 200 parts of ether and allowed to stand for at least 24 hours, whereupon the β -*d*-glucoside tetracetate of desoxycorticosterone crystallises; if necessary, after inoculation. After filtering with suction, washing with ether and drying, 6.6 parts of the glucoside acetate melting at 172°C. are obtained.

The ethereal mother liquors are shaken with a dilute solution of sodium bicarbonate and with water, dried with sodium sulphate, and completely evaporated. For the purpose of saponification the residue is dissolved in 1000 parts of dry methanol, mixed at -15°C. with 10 parts of an approximately 2N-solution of barium methylate, and allowed to stand for 24 hours at the same temperature. The barium ions are then precipitated with the calculated quantity of sulphuric acid. The whole is filtered and evaporated to dryness under reduced pressure, and the resulting viscous mass is shaken with hot water and ethyl acetate, the unchanged starting material being taken up by the ethyl acetate, whilst the free glucoside remains, partly as an oily suspension, in the aqueous layer. The suspension is mixed with an equal quantity of alcohol

and extracted several times with chloroform. After evaporating the chloroform extracts, the residue is dissolved in 29 parts of pyridine and 20 parts of acetic anhydride, allowed to stand for 20 hours, and evaporated at 45°C. under reduced pressure. The residue is dissolved in ether, and the ethereal solution is washed rapidly with hydrochloric acid and water, dried with sodium sulphate, and concentrated. A further 2.2 parts of the β -*d*-glucoside tetracetate of desoxycorticosterone are thus obtained, the total yield amounting to 8.8 parts or 44 per cent. of the theoretical yield.

By using benzene as solvent, instead of chloroform, the yield increases to 60 per cent. of the theoretical yield. On the other hand, K. Miescher, W. H. Fischer and Ch. Meystre [Helvetica Chimica Acta, Vol. 25, page 41 (1941)] obtained a yield of only 25 per cent.

EXAMPLE 5.
10 parts of desoxycorticosterone are caused to react in dry benzene in a manner analogous to that described in Example 4 in the presence of 13 parts of silver carbonate with a solution of 53 parts of acetobromo-maltose in benzene. After filtering the reaction mixture, the filtrate is evaporated, and the residue is dissolved in ether. 9.9 parts of desoxycorticosterone - maltoside heptacetate slowly separate, and after recrystallisation from a mixture of acetone and ether handsome crystals melting at 183—185°C. are obtained.

By saponifying the mother liquors in the manner described in Example 4 the free glucoside is obtained first in the form of a viscous mass, which crystallises on being treated with alcohol. In this manner 2 parts of the β -maltoside of desoxycorticosterone melting at 232—235°C. are obtained. The total yield of the free and esterified maltoside amounts to 42.5 per cent.

EXAMPLE 6.
3 parts of silver carbonate are heated to boiling with 30 parts of benzene. While the benzene is being continuously distilled, a solution of 0.5 part of cis-borneol and 3.25 parts of acetobromo-*d*-glucose in 50 parts of benzene is slowly introduced drop by drop. Heating is continued for a further $\frac{1}{2}$ hour, followed by filtration and evaporation under reduced pressure. The unchanged cis-borneol is expelled with steam under reduced pressure, and the residue so obtained is dried also under reduced pressure. By recrystallisation from a mixture of alcohol and water, and finally from hexane, 0.87

silver carbonate and 25 parts of acetobromo-maltose. The silver salts are removed from the reaction mixture by filtering with suction, and are well washed with acetone. The filtrate is evaporated under reduced pressure, and the residue is saponified by dissolution in 750 parts of dry methanol and admixture at a low temperature with 10 parts of an N-solution of barium methylate in methanol. At the end of 20 hours the barium ions are precipitated with the calculated amount of sulphuric acid. The clear filtrate is then evaporated under reduced pressure, and the residue is shaken with ethyl acetate and water, the unchanged testosterone is taken up by the ethyl acetate and the maltoside, together with the unreacted maltose, by the aqueous liquor. The aqueous portion is mixed with an equal quantity of ethanol, and extracted several times with chloroform. After evaporation of the chloroform extracts under reduced pressure 2.7 parts of the crude testosterone maltoside remain behind.

For purification the crude maltoside is first re-acetylated. For this purpose it is dissolved in 10 parts of pyridine, the solution is mixed with 7 parts of acetic anhydride and allowed to stand for 15 hours at 20°C. The residue obtained by evaporation under reduced pressure at 40°C. is dissolved in ether, and the solution is washed in turn with hydrochloric acid, sodium carbonate solution and water. After drying with sodium sulphate the solution is evaporated, the residue is dissolved in ethanol, and mixed with a little water. The β -maltoside heptacetate of testosterone crystallises in needles melting at 175—180°C.

By saponifying the purified acetate with a solution of barium methylate in 45 methanol the free β -maltoside of testosterone melting at 250—255°C. is

obtained.

Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

1. An improvement in the manufacture of saccharide derivatives of alicyclic or aliphatic alcohols by reacting such an alcohol with an acylhalogenose in the presence of an agent capable of binding hydrogen halides and of a solvent, which consists in continuously removing by azotropic distillation the volatile products split off during the reaction.

2. In the improvement claimed in claim 1, using as the agent capable of binding halogen hydride silver carbonate or silver oxide.

3. In the improvement claimed in claim 1 or 2, adding to the mixture containing the agent capable of binding hydrogen halides one or both of the reaction components at a rate corresponding with the progress of the reaction while the solvent is continuously removed by distillation.

4. In the improvement claimed in claim 1, 2 or 3, using as an alicyclic alcohol an alcohol of the steroid series.

5. A manufacture of a saccharide derivative of an alicyclic alcohol conducted substantially as described in any one of the Examples herein.

6. Saccharide derivatives of alicyclic or aliphatic alcohols whenever prepared or produced by the process of manufacture particularly described and ascertained herein or by any process which is an obvious chemical equivalent thereof.

Dated this 27th day of December, 1944.

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